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Monkeypox Infection: A Rising Public Health Concern

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Abstract

Monkeypox, a zoonotic viral disease, has currently been called a public health emergency by the World Health Organization based on an increasing number of incidents recorded around the globe. Therefore, huge responsibility rests on the shoulders of academicians to disseminate sound knowledge on every aspect of monkeypox. Resultantly raising awareness in the general public about this very disease, this review article circumfuses a brief introduction, history, trends, virology, transmission and diagnosis of monkeypox. It will not only bring to light the zoonotic aspect of monkeypox, its epidemiology and possible consequences on public health but also highlight the role of clinicians and public health professionals in combating this ailment. This review aims to jolt down the precautionary measures, which are to be adopted to limit the spread of monkeypox. It concludes that complete eradication of monkeypox might not be possible because of the fast-mutating virus and reservoir host. Therefore, regular surveillance, vaccination and education of people can be preventive tools in combating monkeypox.



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Introduction

Monkeypox, one of the orthopoxviruses members, reflects smallpox and variola virus in clinical presentation, exhibiting the signs of fever, rash, fatigue and lymphadenopathy [1]. It's a zoonotic viral ailment implying that it is transmittable via saliva, respiratory droplets, and the body fluids from the infected animals to humans. Because of the seclusion of the monkeypox virus from the wild squirrels, those are their reservoir hosts [1]. The Monkeypox virus was first recognized in 1958 after the shipment of primates from Denmark to Singapore. Since the originality, most of the cases of monkeypox virus were in Africa, indicating that it was previously endemic to Africa [2]. Monkeypox was not the talk of the town until its re-emergence in the late nineties and early twenties when it was considered a serious concern for public health. Furthermore, it is citable that countries in addition to Africa reported cases sporadically ascertaining its worldwide distribution and importance. This is the need of the hour to actively include monkeypox in academic research because of the obvious rise in its incidence ever since the 1980's and there is still great room for knowledge about monkeypox [3]. Keeping in view the latest outbreak of this disease and the increasing prevalence, it is a pressing priority to educate the general public about this notable disease and its possible outcomes.

History and Present Status

According to serological tests, monkeys may not be the main source of the monkeypox virus, even though the name derives from the fact that it has been isolated from monkeys [4]. A new name for the disease is being worked on by the World Health Organization (WHO) to stop stigma and racism after the UN health body request of various scientists. They suggested amending nomenclature and changing the name of the virus depending on interhuman transmission is the prospective reason for the flare-up in the European world and North America. It has been stated as "hMPXV" or "human monkeypox virus" by many scientists to distinguish it from viruses existing in African animals. monkeypox virus naming is suggested to be under 3 clades: clade-1 named Congo Basin Clade and clades 2 & 3 as "West African Clade" [5]. West African and Central African are two genetic clades of monkeypox virus. In 1958, a flare-up of a vesicular disease was observed among bound monkeys, which were being transported from Africa for research motives and resulted in the discovery of

monkeypox in the first place. In August 1970, the earliest case report of monkeypox was observed in a small child [6]. The sample was declared positive after viral isolation by WHO Smallpox Reference Centre. The family of the affected child ate monkeys occasionally but not during the last month. Furthermore, the affected child was the only unvaccinated against smallpox in the family [7]. The recent worldwide outbreak is supposed to be the result of the human-to-human transfer. According to the old school of thought, the monkeypox virus is endemic in some African countries. The reference to the virus being African is defaming in the current outbreak [8].

Monkeypox infection can be effectively controlled by the smallpox vaccine, which is proven by the rise of cases of monkeypox infection after the cessation of the smallpox vaccine. The vaccines alone cannot serve in eradicating monkeypox as its spread is dependent upon other factors like the locomotion of animals from one place to the other, intermediate hosts, and other socio-economic conditions. Moreover, vaccine deployment requires some factors, which need to be considered and alternatives must be devised to fully control the spread and morbidity of this disease [9]. Monkeypox was not considered a public health concern in Africa until the late 90s. Following events like the termination of the vaccinia vaccine by WHO, the potential risk of the variola vaccine in patients with HIV, the absence of active surveillance of the monkeypox outbreak and destabilization and movement of masses towards rainforest monkeypox emerged as a larger outbreak in Africa due to secondary transmission with maximum cases recorded in 1996-1997. The use of the variola vaccine as a public health intervention now was limited because it was a concern for HIV patients and more attention was paid to educating the public to control the monkeypox outbreak [10]. Two cases were reported in two individuals who traveled from Nigeria to England in September 2018. These cases are believed to be associated with the monkeypox outbreak in Nigeria at that time and there exists no epidemiological link between the reported cases. Public health measures that were taken in response to the cases being reported included public education, reporting cases to WHO and ECDC, tracing and classifying contacts, conducting surveillance, contacting the exposed individuals over the phone, isolating symptomatic ones, restriction traveling to an exposed population for 21 days and contacting public health personals internationally for effective monitoring of travellers from Nigeria [11]. Seven

confirmed cases of monkeypox were identified in 2022 in England by UKHSA. Surprisingly, 4 out of 7 cases were reported in gays and bisexuals and have no travel history of those countries in which monkeypox is endemic. This situation is a call for concern for clinicians and public health professionals [12]. Even though DNA viruses do not mutate, the monkeypox virus is mutating rapidly probably because of its transmutability in host species. Furthermore, there exists numerous strains of monkeypox virus responsible for the 2022 outbreak. monkeypox virus is believed to be transmitted via the following ways: African rodents (reservoir hosts), direct exposure with the body secretions, skin, bone, and respiratory drops of an infected animal, and interpersonal transmission via respiratory droplets and transplacental route [13, 14].

Virology

Poxviruses have quite a strong propensity to arise outside of their typical biological domain through the transmission to novice populations, given that 50% of the global population lacks immunity against orthopoxviruses [16, 17]. Monkeypox virus belongs to the genus *Orthopoxvirus*, subfamily *Chordopoxvirinae* and family *poxviridae* [18]. Other distinct viruses of the *poxviridae* family, which belong to the same genus are vaccinia; VAC, Variola; VAR and Cowpox; CPV [18, 19]. In 1980, this is declared by WHO that after the extermination of smallpox, monkeypox is considered a pathogenic infection in human beings [20, 21]. Monkeypox virus is a double standard enveloped virus having a genome size of 190kb, which has close pins on both ends and brick shape virion (Fig. 1) [21]. Its genome has close pins on both ends that are encased in a core that is slightly pleomorphic and has a dumbbell form having a diameter of 140-260 nm. More than 180 nucleotides size is covered by various open reading frames (ORF) of the genome [22, 23]. Four more ORFs, that are mostly involved in immunomodulatory functions of host variety willpower along with pathogenicity may be found in the end repeats and different sections that surround the coiled central coding region, which has a size of 56–120 kb [23-25]. Unlike most other DNA viruses monkeypox virus can produce the necessary specific protein for its replication and transcription process [25]. Therefore, their replication occurs in the cytoplasm rather than in the nucleus of the infected cells (Fig. 2). Based on some genotypic, phenotypic, and geographic variations, the virus is separated into two clades, *i.e.*, Congo Basin groups and West Africa;

both groupings have distinct epidemiological and clinical features [26].

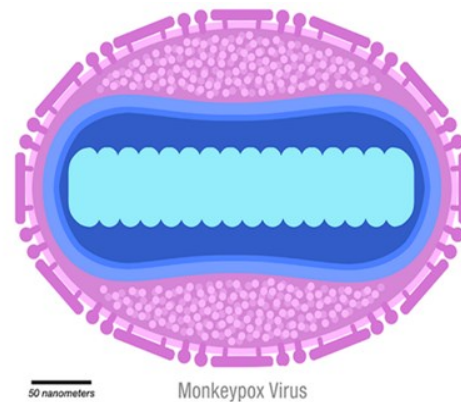


Fig. 1 Membranes and membrane-bound proteins are in purple, capsids are in dark blue, and genomes and nucleoid-associated proteins are in turquoise. Source: Wikipedia https://en.wikipedia.org/wiki/Monkeypox_virus#/media/File:Monkeypox_viruses_scale.png

Epidemiology: Occurrence, Incidence and Regions

Since the first human incidence of the infection was come upon in 1970, monkeypox has become more common, with high-frequency cases being reported in Nigeria, Congo, Cameroon, Liberia, Sierra Leone, Gabon, Sudan, and the Central African Republic. [27-32]. Recently, the sudden prevalence in states such as the UK, US, Israel and Singapore, has been reported to be connected with the African source of the infection [35, 38]. The duplet hereditary clades of the monkeypox virus have been known so far from Central Africa and Western Africa. The Central African clade has been familiar with having 11% case fatality, which is higher in comparison to the Western African clade which is quite less than 1% [33]. The Central African clade has been identified in Congo, Gabon, Sudan, Cameroon and Ivory Coast, whereas the West African clade has been identified in Ivory Coast, Sierra Leone, Liberia, Nigeria, and United States [33-35]. WHO declared that, as the vaccination of smallpox infection was stopped after the eradication of diseases in 1980, it is frequently observed in young individuals between 40-50 years of age (differs with respect to region). The report manifests that many of the monkeypox cases are found in people having the age 40 with a median age of 31 [36]. Besides gender and age distribution of the epidemic have to be investigated. A study in 2017, showed that out of the 36, 26 states of Nigeria were

reported for having monkeypox occurrence, earlier from 11 states recorded an increment [37-39]. Squirrels, rodents and huge pouched rats that act as a reservoir of nourishment in a few regions of the world are the main origins of the virus. [36]. This report has confirmed that males have a 3% higher occurrence compared to females [37]. Direct contact with diseased animals is the main method of disease transmission. Monkeypox is less hazardous than smallpox (30–50%) since it has a lower fatality rate (0–11% cases). The higher percentage is found in humans, mostly in young children and adults who have not had the smallpox vaccine. During the 2003 US outbreak, monkeypox cases were reported in six provinces [40]. The pet prairie dogs were found to be responsible for transmitting the infection, which suggests that they have gained the virus from mammals imported from Ghana into the United States [41]. These infected mammals were placed close to the prairie dogs. An outbreak in Sep. 2018, another kind of human monkeypox was experienced when two traveling Nigerians were identified with the contagion in the UK [35]. A healthcare worker who gained the illness from one of the first two cases was later reported as the third case. This is the main indication present for the inter-human transmission found in monkeypox. Israel reported receiving a shipment of monkeypox from a person who had just emigrated from Nigeria in October 2018 [42]. When a Nigerian immigrated to Singapore in 2019, a similar incident was recorded. This illustrates how important travelers are to the wide impact of infectious disease outbreaks.

Trend and Public Health Emergency

The disease was first identified in the 1970s in the Democratic Republic of Congo, after that, it has also been contracted from the neighboring countries of DRC, like Sudan and many more over time [43]. Other than being endemic in DRC, it has also been declared in Central & West Africa with human and wildlife cases. The disease was thought to be self-limiting and rare, but the present situation is telling a different story [44]. Monkeypox virus was not given full attention until May 2022 when positive cases were detected in most European states as well as South and North America [45]. The alarming thing is the fact that it has been reported in countries where it had not existed for 20 years, which raises questions on the compactness of the biology and epidemiology of the disease. The case fatality rate differs from 1% to 11% [46]. The flare-up of monkeypox is not happening for the first time. It has had outbreaks in

the past. This emerging disease has been reported in 30 countries with more than a thousand cases up till now. Although we have dealt with this virus before, the trend and clinical presentation are atypical. Upon observation, it has been recorded that the disease is more prevalent in individuals who are in their thirties, and more interestingly it is more common in men [46]. Since the vaccination against the smallpox virus has stopped, the incidence of monkeypox has increased as it is believed that humans who are not vaccinated in opposition to orthopoxvirus like smallpox are more prone to getting monkeypox. The chance of getting the disease is most commonly found in people living in forests and kids under 15 years of age [3, 30]. The research on monkeypox was mostly academic-based until the 1980s when the case ratio started to increase and became a public health issue. The chance of it being used as a prospective agent for bioterrorism has also raised public health concerns [48]. The countries through their Integrated Disease Surveillance System have been receiving weekly reports to make a record of the hotspots and better understand the incidence of the disease. The data includes the number of suspected/positive/negative cases, male-to-female ratio, and fatality rate. With all the surveillance systems, it is believed that only 10 percent of the positive cases are making up to the record at the national level, which weakens the reliability and authenticity of the epidemiological studies [44].

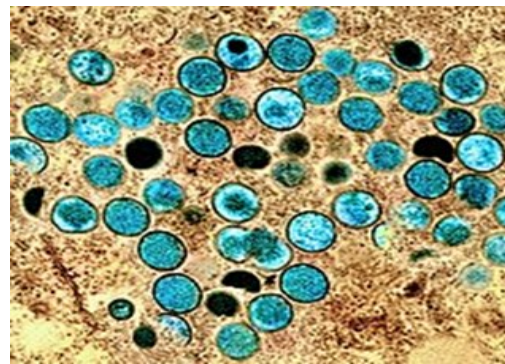


Fig. 2 Colourful transmission electron micrograph of monkeypox particles (teal) found within an infected cell (brown) cultured in the laboratory. Source: Wikipedia [https://en.wikipedia.org/wiki/Monkeypox_virus#/media/File:Monkeypox_Virus_\(52103767506\).jpg](https://en.wikipedia.org/wiki/Monkeypox_virus#/media/File:Monkeypox_Virus_(52103767506).jpg)

Monkeypox Virus: A Neglected Zoonotic Pathogen Spread Globally

The causal agent of zoonotic monkeypox is a DNA virus named MPXV, which is characterized into

duplet hereditary clades, West African clades and Congo Basin clades. The incubation time of the virus range from four-twenty-one days. The clinical demonstration of this virus has many similarities with smallpox and the differential point between these two diseases is lymphadenopathy [48, 49]. Monkeypox is originated and limited to African countries until it spread to non-African countries which rings alarm bells. This virus is not that deadly and people having strong immunity surpass it but people have weakened immune systems, aged individuals, neonates and expecting women may develop detrimental effects [49]. In 2019, case reports of monkeypox were documented only in southern Nigeria but now they are being reported in the whole of Nigeria [50]. This change in the dynamics of the disease is due to an unjust supply of community well-being assets, an increased inspection of Lassa fever flare-ups, COVID-19, residential areas close to forests, and a shift from rural to urban areas.

The main cause of its spread in non-endemic areas is still unexplored. Until the times cases appeared on the public health scale, several interhuman transmissions have occurred that it would not be possible to follow back the main cause. The following factors are enlisted that may account for the unnoticed cause: cases not being reported, monkeypox not being properly diagnosed as a sexually transmitted disease, moderate or subclinical cases and lack of operating inspection for monkeypox. Up until this point, no advanced alternative of monkeypox virus has been identified and outline genetic makeup represents no diminish in the content and extent of the genome that predicts raised virulency in the smallpox virus. Furthermore, all of the monkeypox virus isolated from 2022 cases belong to the Western African clade [49]. A phylogenomic study conducted in 2022 with the monkeypox virus secluded from multiple countries indicates the perpetual increase in the progression of the virus in anthropoids as per isolation in the unique genealogical branch [51, 52]. Although the present research should be cross-matched with repeated timescale phylodynamic evaluation and additional replacement rates every year must be deducted from the monkeypox virus genetic make-ups, which are being secluded from the 2022 monkeypox. The above-mentioned study results were previously hypothesized by Kugelman [53]. The possible factors for the latest dissemination of monkeypox virus across the world could be due to the stoppage of vaccination in 1980. Demographics showed that mostly the infected persons are aged fifty years, or

under & vaccination with non-amplifying MVA-BN (JYNNEOS or Imvanex) has a protective effect. [49]. Other possible factors include a rising incidence of monkeypox cases in endemic areas and a bigger possibility that the virus can be exported leading to its global spread, climate change and lack of active surveillance [54]. Rapid actions must be undertaken to avoid the development of monkeypox in household and wild animal communities in recently non-endemic areas. Recently, no such proof of human-to-animal transmission was found as per WHO [57]. Monkeypox virus is promiscuous, *i.e.*, can infect numerous animals. The ensuing measures should be adopted worldwide so that its spread could be stopped: administration of smallpox vaccine, provision of cross-protection in opposition to monkeypox to high risk persons; post-openness vaccination in earlier infested animals; operating monkeypox inspection in residents of endemic areas; time-to-time epidemiological inspection of monkeypox in lab animals and little warm blooded creatures; community well-being governing check beyond trade and holder of pet lab animals, little warm blooded creatures as well as other wild animals; detailed individual connection tracking and the particular monkeypox virus source should be detected. Detection of the source will support filling research gaps about virus ecology, development, and communication dynamics [49]. Last but not the least, endemic areas must be prioritized and focused. The recent increasing prevalence of monkeypox virus in non-endemic areas is alarming and indicates the loopholes in public health policies for endemic areas like sub-Saharan Africa which should be prioritized. Furthermore, zoonotic pathogens like monkeypox spread like fire in today's global world if not paid attention.

Diagnosis of Monkeypox Virus

In 1970, the earliest case of monkeypox was reported from Zaire in 9-month-old children [58, 59]. In the US in 2003, human infection with monkeypox emerged when imported African animals infected pet dogs [59]. Two cases of monkeypox were reported in the US in September 2018, which ultimately cause nosocomial infection in nurses [11, 59]. For the diagnostic approaches, the pustules samples are processed in PCR and transmission electron microscopy techniques (Table 1). For electron microscopy, particulates were enhanced before being negatively stained with phosphotungstic acid. Several brick-shaped particulates, a hallmark of orthopoxviruses, were found in the sample [59, 60].

Table 1 Diagnostic tests used for monkeypox virus.

Tests	Advantages	Disadvantages	Sensitivity	Specificity	References
ELISA	Practical in endemic regions	Technically complex Recent vaccination interferes with testing	Low	High	[74-77]
RT-PCR	Rapid detection	Need special equipment	High	High	[78, 79]
Cell culture	Vaccine study	Not used commonly	-	-	[42, 80]
Immunohistochemistry	-	Not routinely used	-	-	[81]
Electron microscopy	Evaluate specimens for all progeny virions	Not used	-	-	[83]

This virus can infect humans when they come into contact with an infected animal's body fluids or abscesses. Large respiratory droplets from an infected animal can spread the disease from direct contact although it does so far less effectively than smallpox does [61]. The clinical representation of monkeypox much resembles the clinical picture of smallpox [63]. In most of the patients of monkeypox before rashes, some significant signs like fever, enlargement of submandibular, cervical and inguinal lymph nodes, and malaises appear [63, 64]. Other specific signs and symptoms of monkeypox involve headache, backache, chills, sore throat cough, sweats, and difficulty in the breath. The distinctive key feature of monkeypox is lymphadenopathy, which is mostly observed in more than 90% of the non-vaccinated candidates [61]. As chickenpox, smallpox and monkeypox have quite similar clinical representation, precise diagnosis is the key factor to keeping such naturally occurring diseases under control [65]. Even though the clinical picture is useful in the diagnostic approach of monkeypox infection from other vesiculopustular rashes, for the definitive diagnosis laboratory tests are required. This includes direct detection by electron microscopy, vesicular lesion swabs, histopathological analysis, orthopoxvirus real-time PCR, immunofluorescent antibody assay, phylogenetic analysis, ELISA, and virus isolation (Table 1) [66]. But some of these procedures are comparatively general and are impotent to distinguish among monkeypox and poxviruses infections [67]. Histologically many lesions resemble other viral exanthems, but in terms of the immunochemistry analysis, it will be able to distinguish pox virus infection from the herpes virus [68]. Under electron microscopy, the morphology of the virion of the poxvirus is specifically shows a brick like shape along with lateral bodies and a central core [65, 66, 69]. According to recent studies, lesions of monkeypox virus X under a microscope show keratinocytes with massive numbers of mature and immature virions in an assembled way [69].

Monkeypox virus can be identified through virus isolation; in mammalian cell cultures, the virus has been cultivated. PCR is tracked by analysis or the sequencing of amplicons of restriction fragment length polymorphism. PCR also detects the monkeypox virus and primer sets based on consensus sequences around or at the last of the monkeypox haemagglutinin sequence can discriminate monkeypox virus from others pox viruses [70, 71]. In monkeypox virus, viremia is associated with leukocytes [72]. Epidermal Langerhans cells are more prone to monkeypox infection. They served as the vehicle for transmitting the virus approaching the regional lymph nodes and ultimately result in lymphadenopathy [73]. Moreover, the presence of the anti-poxvirus ab in an individual who is not vaccinated yet has a history of illness and rashes, vesicles, and pustules lead to the suggestion of the diagnosis of monkeypox. In conclusion, the histologic characteristics of the infection must be included in the diagnosis of the dermatopathology repertoire relatively than being attributed to another viral process considering the recent introduction of the monkeypox [82].

Disease Control and Preventive Measures

When the disease is diagnosed, the only effective public protective precautionary measures are to quarantine and to go for the immediate ring vaccination. This is for there's no sufficient operative certified therapy for monkeypox. Lesions, vesicle swabs, and other cutaneous tissues should be handled carefully and their collection should be done by aseptic protocol with respiratory safety. This is because monkeypox virus transmission is mostly done by direct methods and aerosol particles [89]. In 1960s, researchers showed that vaccination with smallpox may successfully immunize monkeys against monkeypox [90]. Combined vaccination along with aggressive surveillance results in the

complete eradication of smallpox worldwide. Monkeypox cannot be completely eradicated since there is an animal reservoir for the disease but the smallpox virus vaccine is quite active in averting monkeypox virus infection [91, 92]. In Africa, many vaccinated persons in cases are observed with mild lesions of monkeypox infection and some cases are in subclinical form [93]. Because of these reasons, centres for disease prevention and control advice pre-exposure immunization for individuals involved in human as well as animal monkeypox investigations, medical personnel treating monkeypox patients, anyone in close contact with potentially monkeypox-infected animals and laboratory personnel handling potentially infected specimens [94]. Antivirals like cidofovir and brincidofovir, tecovirimat are found active in opposition to monkeypox virus infection. The US Food and Drug Administration (FDA) approved that tecovirimat and cidofovir for the treatment of monkeypox under extended access protocol. Smallpox vaccination with JYNNEOSTM and ACAM2000® vaccines may safeguard against monkeypox virus and improve therapeutic symptoms [95]. There is no specific cure or immunization against monkeypox virus infection now. As stated earlier, few animals' examination recommends that few of the vaccine of the smallpox had been revealed to be valuable against monkeypox 2 and can weaken disease consequences as post-exposure prophylaxis [95]. Due to the reported negative consequences, especially in immune-suppressed individuals, replicating smallpox vaccinations ought not be utilized to inoculate against the monkeypox virus. It might likewise elevate the gamble of recombination among V and the antibody strain, in a coinfecting or superinfected person. Although, smallpox vaccines by altering must not be utilized for vaccination against monkeypox infection because of the reported unfavourable consequences, especially in individuals who are immune-compromised, and it can also increase the threat of recombination between V in superinfected person. One of the main forces influencing the evolution of orthopoxviruses is recombination, although it is challenging to predict how recombinants are challenging to foresee. Most patients have a moderate infection and recover without medical help, but in highly immune-compromised individuals, medication with antivirals or varicella immune globulin can be used [96].

Conclusions

In a nutshell, monkeypox disease, which originated in Africa, has now become a public health catastrophe

due to higher case counts being recorded in other parts of the globe. Owing to its zoonotic nature, it is a matter of public health concern. However, no appreciable research has been conducted to date regarding its potential threats to wildlife veterinarians as an occupational hazard. The fact that new cases are being recorded in bisexuals and the LGBT+ community is also surprising and needs to be explored further. Also, research must be undertaken to find out the source of its multi-community spread. Monkeypox cannot be completely eradicated from the world because of its reservoir host and fast mutating virus but regular surveillance coupled with vaccination and education of people about this disease can serve as preventive tools in combating monkeypox.

Conflict of interest

The authors declare no conflict of interest.

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